REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 29-31 are requested to be canceled. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

Claim 28 is currently amended.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Upon entry of this Amendment, claims 1-28 and 32-52 will remain pending in the application.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Response to Issues Raised by Examiner in Outstanding Office Action

a. Objection under the Sequence Rules

The Office objected to the specification for not providing a SEQ ID NO in the description of Figure 15(A-C). See Office Action, pp. 2-3. Applicants have inserted the appropriate SEQ ID NO identifiers and request withdrawal of the objection.

b. Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 28-40 are rejected by the Examiner under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. Applicants have amended claim 28 to add a "wherein" clause indicating that the method achieves the results provided in the preamble. See Office Action,

pp. 6-7. In light of these amendments, Applicants respectfully request reconsideration and withdrawal of the rejection.

c. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 28 and 30-40 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph for lack of enablement. The Office has conceded that the specification is enabled for the a method "wherein the subject has allergic asthma" and "wherein the method substantially reduces or depletes macrophages in said subject." See Office Action p. 4. Applicants have amended claim 28 to recite the subject matter conceded as enabled. In light of these amendments, Applicants believe the concerns of the Office have been addressed. Applicants respectfully request reconsideration and withdrawal of the rejection.

d. Claim Rejections - 35 U.S.C. § 103

Claims 28, 29 and 32-40 are rejected by the Examiner under 35 U.S.C. § 103 as being obvious over Bruhle, in view of Schuh and Blease. The Office asserts:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the anti-CCR5-anti-CD3-bispecific ab or the chimeric fusion protein RANTES-PE38 to deplete CCR5 expressing cells as taught by Bruhl in a method for reducing/depleting macrophages in a human suffering from allergic asthma with a reasonable expectation of success. The motivation and expected success is provided by Bruhl, Schuh, and Blease. Bruhl teach that anti-CCR5-anti-CD3-bispecific antibodies and RANTES-PE38 fusion protein efficiently depletes CCR5 positive cells and that CCR5 is expressed on moncytes/macrophages. Schuh teach that CCR5 and RANTES are key contributors to the development of chronic lung asthma and administered anti-RANTES antibodies reduced the hallmarks of allergic asthma in a mouse model for chronic fungal asthma. Blease demonstrate that a chimeric fusion protein comprising IL-13 and Pseudomonas exotoxin (IL-13-PE38QQR) can be administered intranasally and reduce chronic fungal allergic airway disease in mouse model. It would be obvious to employ the claimed method in humans because Bruhl teach the depletion of macrophages and that RANTES-PE38 fusion protein is a useful agent in the treatment of chronic inflammatory disease and Schuh, who teach the successful treatment (reduction of peribronchial cell infiltrates) in an animal asthma mouse model upon administered anti-RANTES antibodies.

Office Action, pp. 10-11.

To establish a *prima facie* case of obviousness, there needs to be (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) the prior art references, when combined, must teach or suggest all the limitations of the claimed invention. *See* MPEP §2143 (Aug. 2001). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully assert that the Office has not met its burden.

The claims recite a method of treating allergic asthma comprising identifying a subject in need of reducing macrophages and administering to the subject a pharmaceutical composition comprising a chimeric polypeptide that comprises a moiety that specifically binds to a CCR5 and a second polypeptide domain.

Bruhl report studies of a RANTES-PE38 fusion protein and its effect on $CCR5^+$ CHO cells *in vitro*. Bruhl concludes that the fusion protein is internalized by the $CCR5^+$ cells, and that the PE38 toxin retains its cytotoxic activity, killing the cells. The authors suggest that the fusion protein may be useful for treating chronic inflammatory diseases. See, Bruhl, pp. 2424-5. Nothing in Bruhl teaches or suggests the use of a RANTES-PE38 fusion protein for the treatment of allergic asthma as recited in the claims.

Schuh teaches a method in which anti-RANTES antibody is used for treating allergic asthma. Schuh reports that anti-RANTES antibodies curtailed leukocyte and eosinophil recruitment in mice, concluding that neutralization of RANTES/CCL5 further reduced the hallmarks of allergic asthma. See Schuh, p. 230.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use the RANTES-PE38 fusion protein in combination with anti-RANTES antibodies described in Schuh to treat allergic asthma. See Office Action, pp. 10-11. Applicants disagree. Administration of a RANTES-PE38 fusion protein, as in the pending claims, activates RANTES receptors. This is confirmed by studies demonstrating that upon the administration of a RANTES-PE38 fusion protein, more macrophages and eosinophilic

granulocytes were detected in the lung.[1] Thus the RANTES-PE38 fusion protein elicits its biological effects not by neutralization of RANTES, as would the anti-RANTES antibody described in Schuh, but by activating RANTES receptors and depleting certain RANTES-PE38 sensitive cells.

In short, Bruhl discloses that a therapeutic benefit is achieved by administering a RANTES polypeptide, whereas Schuh discloses that a therapeutic benefit is achieved by neutralizing RANTES using a RANTES antibody. Applicants therefore assert that one skilled in the art would not be motivated to combine a RANTES-PE38 fusion protein, with an anti-RANTES antibody, especially given the findings that the RANTES-PE38 fusion protein increases macrophages and eosinophilic granulocytes and, in contrast, the anti-RANTES antibody curtailed leukocyte and eosinophil recruitment.

For the reasons described above, Applicants assert that neither the teachings of Bruhl or Schuh either alone or in combination would lead one of skill in the art to administer such a chimeric polypeptide for the treatment of allergic asthma as recited in the claims.

The Office also cites Blease for its teachings regarding the administration of a specific IL-13-PE38 fusion protein. However, Blease does not remedy the shortcomings of Bruhl and Schuh because Blease makes no connection between CCR5, allergic asthma, and the reduction of macrophages. Applicants therefore assert that the combined teachings of Bruhl, Schuh and Blease do not support a *prima facie* case of obviousness.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

[1] See European Journal of Immunology 33 (2003), 3080-3090, copy attached. Intranasal RANTES-PE38 treatment enhanced macrophage recruitment. (See abstract.)

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 4/27/07

By [signature] Reg 59,349

for Richard Peet
Attorney for Applicant
Registration 35,792

FOLEY & LARDNER LLP
Customer Number:
22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5483
Facsimile: (202) 672-5399